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ExxonMobil
Chemical

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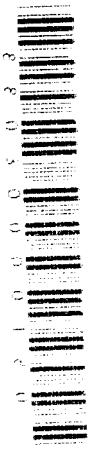
Document Processing Center (7407M)
Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics,
Environmental Protection Agency
1200 Pennsylvania Avenue, NW,
Washington, DC 20460-0001

Contain NO CBI

Re: Notification Under TSCA Section 8(e)

Dear Sir or Madam:

Under the provisions of Section 8(e) of the Toxic Substances Control Act (TSCA), ExxonMobil Chemical Company is submitting the following information describing the toxicity of a substance described as 1,2-Benzenedicarboxylic acid, di-C_{6-8} branched alkyl esters, C_7-rich (CAS Registry Number 71888-89-6). This substance is currently being manufactured for commercial purposes as defined by TSCA.



The data presented in this submission are from a two-generation reproductive toxicity study in rats. The study protocol followed that described in the U.S. EPA, Health Effects Test Guidelines; OPPTS 870.3800: Reproduction and Fertility Effects (Aug. 1998). A one-generation range finding study preceded this two-generation study and the results of this two-generation study are summarized in the attachment. A copy of the two-generation study final report will be submitted when it becomes available.

In brief, the study demonstrates developmental effects attributed to the test substance. Findings were chiefly in male secondary sex organ development in the F_1 and F_2 generations, reduced anogenital distance and delays in preputial separation for 8000 ppm dose level pups and similar findings into the 4500 ppm dose level in the F_2 generation. There were F_1 males with hypospadia and swelling of the prepuce in the 8000 ppm group. Three F_1 animals had an undescended testis, two at 8000 ppm and one at 1000 ppm.

The deficiencies of anatomic development in the F_1 generation may have been the chief contributing factors in reduced reproductive performance (mating and fertility indices) at the 4500 ppm and 8000 ppm dose levels. Quantifiable reproductive effects in the F_1 generation were reduced sperm production rates and reduced testicular sperm concentrations at all dose levels but did not affect mating or fertility at 1000 ppm. Although the findings appeared to be treatment-related, they were not dose-related and showed considerable numeric variation in the inter-generation comparison. No treatment-related effects were seen in the F_0 generation and F_1 control values were approximately 23 percent higher than F_0 control values. There were no test article-related effects on the percentages of motile and progressively motile sperm or absolute number and percentages of morphologically normal sperm at any dose level.

It is our understanding from previous Section 8(e) guidance from EPA that reproductive effects at dose levels greater than 250 mg/kg/day are considered to be of low concern and should generally

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not be submitted under Section 8(e). As shown in the table below, only the findings of reduced sperm production rate/reduced testicular sperm concentration and the single animal with an undecended testis at the in the F_1 1000 ppm level would be considered of medium concern. It should be noted that estimated human exposures from commercial use of this substance are well below the dose levels tested in this study.

Female Parental Exposure		Dosage				
Period	**Generation**	**PPM**	**0**	**1000**	**4500**	**8000**
Gestation	F_0	mg/kg/day	0	64	304	532
Lactation	F_0	mg/kg/day	0	162	716	1289
Gestation	F_1	mg/kg/day	0	64	309	543
Lactation	F_1	mg/kg/day	0	168	750	1360

Although the observations here are for 1,2-Benzenedicarboxylic acid, di-C_{6-8} branched alkyl esters, C_7-rich, similar findings have been reported for related 1,2-Benzenedicarboxylic acid, di-C_{4-8} branched alkyl esters. Some of these data have recently been reviewed by the Center for the Evaluation of Risks to Human Reproduction (CERHR)[1].

The current rodent study results are put into context with respect to their relevance to man by a recent comprehensive study in marmosets.[2] In that study, juvenile marmosets were exposed to up to 2500 mg/kg/day of 1,2-Benzenedicarboxylic acid, di- (2-ethylhexyl) ester for over 65 weeks, from weaning to sexual maturity. No effects were seen on sperm parameters or the male reproductive tract.

Sincerely,

Glenn A Grotz/AKF

Attachment

[1] http://cerhr.niehs.nih.gov/news/phthalates/dbp-final-inprog.PDF
http://cerhr.niehs.nih.gov/news/phthalates/DEHP-final.pdf

[2] Tomonari Y et al. (2003) Testicular Toxicity Study of Di(2-ethylhexyl) phthalate (DEHP) in juvenile common marmoset. 42nd Annual Society of Toxicology Meeting (SOT) Meeting Abstract.

Summary Information

Background and Findings

- A dietary Two-Generation Reproductive Toxicity study was conducted in rats with 1,2-Benzenedicarboxylic acid, di-C_{6-8} branched alkyl esters, C_7-rich (CAS# 71888-89-6) to evaluate the potential for adverse effects of the test article on the reproductive capabilities encompassing gonadal function, estrous cyclicity, mating behavior, conception, gestation, parturition, and lactation in the F_0 and F_1 parental generations. The F_1 and F_2 weanling generations (pups) were evaluated for neonatal survival, growth and development. The protocol followed current guidelines[1].

- Test article was offered in diet continuously to both sexes (30/sex/dose) for a minimum of 70 days prior to mating and continued during the mating (F_0 and F_1), gestation and lactation periods until scheduled termination of the adults and/or pups (F_1 and F_2).

- Test article concentrations were 0, 1000, 4500, or 8000 ppm in feed and the consumption equated to dosages (mg/kg B-Wt/ day) for the various intervals of the study as follows:

Mean Calculated Test Article Consumption
(mg/kg b-wt/day)*

F_0 Generation		**MALES**		**FEMALES**		
	Target Dose Level (ppm)	Prior to Breeding	After Breeding	Prior to Breeding	Gestation Period	Lactation Period
	0	0	0	0	0	0
	1000	81	50	89	64	162
	4500	343	222	406	304	716
	8000	623	404	726	532	1289
F_1 Generation						
	0	0	0	0	0	0
	1000	91	50	100	64	168
	4500	416	227	462	309	750
	8000	764	419	833	543	1360

* Summation of Mean Compound Consumption for Specified Interval / Number of Periods (weeks or daily intervals) Assessed.

- **Findings:**
  Treatment-related developmental findings were chiefly in male secondary sex organ development in the F_1 and F_2 generations, reduced anogenital distance and delays in preputial separation for 8000 ppm dose level pups and similar findings into the 4500 ppm dose level in the F_2 generation. There were F_1 males with hypospadia and swelling of the prepuce in the 8000 ppm group. Three F_1 animals had an undescended testis, two at 8000 ppm and one at 1000 ppm.

  Quantifiable reproductive effects in the F_1 generation were reduced sperm production rates and reduced testicular sperm concentrations at all dose levels. Although the findings appeared to be treatment-related, they were not dose-related, and showed considerable numeric variation in the inter-generation comparison. No treatment-related effects were seen in the F_0 generation and F_1 control values were approximately 23 percent higher than F_0 control values). There were no test article-related effects on the percentages of motile and progressively motile sperm or absolute number and percentages of morphologically normal

[1] OECD Guidelines for Testing of Chemicals; Method No. 416: Two-Generation reproduction Toxicity Study (Jan. 22, 2001) and U.S. EPA, Health Effects Test Guidelines; OPPTS 870.3800: Reproduction and Fertility Effects (Aug. 1998)

sperm at any dose level. However, mating or fertility was not affected at 1000 ppm suggesting that the deficiencies of anatomic development in the F_1 generation may have been the chief contributing factors in reduced reproductive performance (mating and fertility indices) at the 4500 ppm and 8000 ppm dose levels.

GROUP	Control	1000 (ppm)	4500 (ppm)	8000 (ppm)
Mean Sperm Production Rates (Millions / Gram / Day)				
F_0	12.4 ± 3.04	-	-	13.6 ± 1.78
F_1	15.3 ± 2.43	9.3 ± 2.43	9.4 ± 3.53	8.1 ± 7.26
Left Testis Sperm Conc. (Millions / Gram)				
F_0	75.9 ± 18.55	-	-	83.2 ± 10.85
F_1	93.2 ± 14.81	56.7 ± 14.8	57.6 ± 21.56	49.5 ± 44.28

There were dose-related increased liver and kidney weights (both sexes F_0 and F_1 parental animals) in the 4500 ppm and 8000 ppm groups and increased pituitary weights for F_1 males at 8000 ppm. Histopathologic findings in liver, kidney and pituitary included centrilobular hepatocellular hypertrophy, hepatocellular vacuolation, dilated renal pelves / hydronephrosis and hypertrophy within the pars distalis for F_1 generation animals. There were, at the 8000 ppm dose level, decreased gonadal weights in the F_1 generation for both sexes and decreased secondary sex organ weights for males. There were significantly reduced offspring body weights and weight gains noted in F_1 pups in the 8000 ppm group and F_2 pups in the 4500 ppm and 8000 ppm groups.

The toxicity findings were of medium and low concern and are as follows:

- Reduction in anogenital distance in F_1 males (8000 ppm) on PND 1.
- Reduced anogenital distance F_2 males (4500 ppm and 8000 ppm) PND 1.
- Retention of thoracic nipples F_1 males (8000 ppm) on PND 11, 12, and 13.
- Delayed acquisition of balanopreputial separation F_1 males (8000 ppm) 50.3 days vs. 41.6 days for controls.
- External genitalia effects in F_1 males (5/28 hypospadias and 5/28 swelling of the prepuce at 8000 ppm).
- Undesended testes/testis in F_1 males (1/28 at 1000 ppm and 2/28 at 8000 ppm).
- Decreased spleen weights (absolute and relative) for F_1 pups (females; 4500 ppm and males/females; 8000 ppm).
- Reduced F_1 reproductive performance (mating indices: 8000 ppm males at 67.9% and females at 63.3%).
- Reduced F_1 reproductive performance (fertility indices: 4500 ppm males and females at 69.0%; and 8000 ppm males at 42.9% and females at 40.0%).
- Reduced gestation body weight gain F_1 females (8000 ppm) GD 0-4.
- Reduced body weight F_1 females (8000 ppm) GD 4, 7, 11, 14 and PND 0, 17, 20.
- Reduced F_1 sperm production rates and testicular sperm concentrations (1000, 4500 and 8000 ppm).
- Decreased gonadal weights in both F_1 sexes and F_1 male weights of seminal vesicle/coagulating gland, prostate, and epididymis (8000 ppm).
- Absence (complete, unilateral or segmental) of testes, prostate, seminal vesicles, vas deferens, coagulating gland and/or epididymides in F_1 generation (4500 and 8000 ppm).
- Increased kidney weights F_1 males (4500 ppm and 8000 ppm) groups.
- Dilated renal pelves and hydronephrosis (4500 ppm and 8000 ppm) in F_1 males.
- Increased pituitary weight F_1 males (8000 ppm).
- Increased liver weights F_1 females (4500 ppm and 8000 ppm) and male relative liver weights (8000 ppm).
- Hepatocellular centrilobular hypertrophy F_1 males (4500 ppm) and males and females (8000 ppm).
- Hepatocellular vacuolation F_1 males (4500 ppm and 8000 ppm).
- Reduced F_2 offspring body weight gain PND 7-14 and 14-21 for females (4500 ppm) and males and females (8000 ppm).
- Decreased spleen weights F_2 males and females (4500 ppm and 8000 ppm).
- Increased relative brain weights F_2 males (4500 ppm) and males and females (8000 ppm).